In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: July 30, 2019

ERMERITA MORALES, *Mother and natural guardian of* M.S.M., *a minor*,	*	PUBLISHED
Petitioner,	*	No. 14-1186V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Diphtheria-Tetanus-acellular Pertussis ("DTaP"); Haemophils Influenzae Type B ("Hib"); Inactivated Polio ("IPV"); Pneumo -coccal Conjugate ("PCV"); Hepatitis B ("Hep B"); Rotavirus; Febrile Status Epilepticus; Encephalopathy; Challenge -Rechallenge; Absence of SCN1A Mutation.
Respondent.	*	

Clifford J. Shoemaker, Shoemaker, Gentry & Knickelbein, Vienna, VA, for petitioner.[1]
Christine M. Becer, United States Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[2]

On December 10, 2014, Ermerita Morales ("petitioner"), on behalf of her minor child M.S.M., filed a petition for compensation under the National Vaccine Injury Compensation

[1] While Mr. Shoemaker has been petitioner's attorney of record throughout this claim, another attorney, Mr. J. Robb Cecil has provided invaluable assistance. He was the first attorney contacted by petitioner, whose primary language is Spanish. Mr. Cecil referred the case to Mr. Shoemaker, but stayed involved to facilitate communication between petitioner and her counsel, her expert, and her medical providers. Tr. 4-5. Mr. Cecil appeared at the entitlement hearing and was admitted as co-counsel *pro hac vice*. I thank him for his contributions to this case.

[2] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), because this opinion contains a reasoned explanation for the action in this case, I am required to post it on the website of the United States Court of Federal Claims. The court's website is at http://www.uscfc.uscourts.gov/aggregator/sources/7. **This means the opinion will be available to anyone with access to the Internet.** Before the opinion is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). An objecting party must provide the court with a proposed redacted version of the opinion. *Id.* **If neither party files a motion for redaction within 14 days, the opinion will be posted on the court's website without any changes.** *Id.*

Program.[3] Petition (ECF No. 1). On March 11, 2013, at approximately six months old, M.S.M. received vaccinations for diphtheria-tetanus-acellular pertussis ("DTaP"), haemophilus influenza type B ("Hib"); inactivated polio ("IPV"); pneumococcal conjugate ("PCV"); hepatitis B ("hep B"); and rotavirus. Within approximately 16 hours, M.S.M. developed a fever and status epilepticus. On December 26, 2013, M.S.M. again received DTaP, Hib, and PCV vaccinations, then developed fever and status epilepticus again within a similar period of time. M.S.M. did not have developmental delay prior to the initial seizure activity in March 2013; she did afterwards. She continues to have seizure activity. Genetic testing was negative for known pathogenic mutations in SCN1A and other genes associated with seizure disorders.

Petitioner alleges that M.S.M.'s vaccines caused an acquired epileptic encephalopathy. Petition; *see also* Petitioner's ("Pet.") Pre-Hearing Brief (ECF No. 82) at 19, 29; Pet. Post-Hearing Brief (ECF No. 123) at 55.[4] She and her experts present various theories, including that an innate immune response can and did cause fever and status epilepticus, which lowers the threshold for further seizures.

After a review of the entire record, I find that petitioner has presented preponderant evidence that M.S.M.'s vaccinations caused an encephalopathy which is responsible for sequelae including her developmental delay and continued seizure activity. She has satisfied her burden of proof. Accordingly, she is entitled to compensation.[5]

I. Procedural History

Petitioner filed her claim on December 10, 2014. The parties and I agreed that M.S.M. should undergo two rounds of genetic testing, which was negative for any known pathogenic mutations. Petitioner's Exhibits ("Exs.") 17, 63. Respondent still recommended against compensation on the grounds that petitioner had not presented preponderant evidence that M.S.M.'s injuries were caused by the vaccinations and were more likely caused by an

[3] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-1 to 34 (2012) ("Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

[4] The current Vaccine Injury Table creates a presumption of causation if pertussis vaccine (DTP, DTaP, P, DTP-Hib) is followed within 0 – 72 hours by an acute encephalopathy that meets certain criteria. For a child who is less than eighteen months old upon receiving pertussis vaccination (such as M.S.M.), "an acute encephalopathy following a seizure is demonstrated by a significantly decreased level of consciousness that lasts at least 24 hours and cannot be attributed to a postictal state from a seizure or medication." 42 C.F.R. §§ 100.3(a), (c)(2)(i). In this case, M.S.M. did receive pertussis vaccine and experienced an encephalopathy within 72 hours thereafter. However, petitioner does not allege a Table injury. *See* Pet. Post-Hearing Reply (ECF No. 130) at 15, n. 5 ("Petitioner is not arguing that M.S.M. meets the Table definition for encephalopathy"). Upon review, I find that M.S.M. likely does not meet that criteria because following her March 11, 2013 febrile seizure, she did not exhibit a significantly decreased level of consciousness for at least 24 hours. However, she has established an off-Table encephalopathy.

[5] Pursuant to Section 13(a)(1), in order to reach my decision, I have considered the entire record, including all of the medical records, expert testimony, and literature submitted by the parties. This opinion discusses the elements of the record I found most relevant to the outcome.

"unidentified genetic mutation." Respondent's Rule 4(c) Report ("Resp. Rep't") filed February 26, 2016 (ECF No. 41).

Both parties retained experts in support of their respective positions. Petitioner submitted several reports from Dr. Yuval Shafrir.[6] Pet. Exs. 18, 64, 90, 92. Petitioner also submitted one report from Dr. Joseph Bellanti.[7] Pet. Ex. 95. Respondent submitted one report from Dr. Max Wiznitzer.[8] Resp. Ex. B. Respondent also submitted two reports from Dr. Francis Lobo.[9] Resp.

[6] Dr. Shafrir is board-certified in neurology with a special qualification in pediatric neurology. Pet. Ex. 19 at 2. He is also certified by the American Board of Clinical Neurophysiology, which relates to special expertise in epilepsy and EEG testing. Dr. Shafrir stated that this certification qualifies him as an "epileptologist." Pet. Ex. 19 at 2; Tr. 11. Dr. Shafrir received his medical degree *magna cum laude* from the Sackler School of Medicine in Tel Aviv in 1982. Pet. Ex. 19 at 1. After medical school, he completed several years of pediatric training in Israel, followed by a residency in pediatrics at North Shore University Hospital, which is affiliated with Cornell University Medical College. *Id.* He then completed a pediatric neurology residency and fellowship at Washington University in St. Louis, followed by an epilepsy fellowship at Miami Children's Hospital in Miami, Florida. *Id.* He then worked as a pediatric neurologist at Walter Reed Army Medical Center, Georgetown University Hospital, and the Oklahoma University Hospital. In 2000, he opened a private practice, which has since been acquired by Sinai Hospital in Baltimore, Maryland. *Id.* at 2; Tr. 11. He is also an assistant professor teaching pediatrics and neurology at the University of Maryland in Baltimore, Maryland. Pet. Ex. 19 at 2. At the entitlement hearing, I granted petitioner's unopposed motion to admit Dr. Shafrir as an expert in pediatrics and epileptology. Tr. 12. As noted in the summary of relevant facts, Dr. Shafrir also met with petitioner and M.S.M. to provide a second opinion on her care in January 2015. Dr. Shafrir drew from that evaluation in his first expert report, dated January 30, 2015.

[7] Dr. Bellanti is board-certified in pediatrics as well as allergy and immunology. Pet. Ex. 96 at 4. He received his medical degree from the University of Buffalo in Buffalo, New York in 1958. Pet. Ex. 96 at 4. He then spent several years practicing pediatric medicine at several hospitals in the Buffalo area. *Id.* He spent one year as a National Institutes of Health special trainee in immunology at the University of Florida, followed by two years as a research virologist at the Walter Reed Army Institute of Research. *Id.* In 1963, Dr. Bellanti was hired by Georgetown University, where he has since been a treating pediatrician; a researcher; and a professor of pediatrics, immunology, and microbiology. *Id.* He teaches medical students as well as fellows at the university's International Center for the Interdisciplinary Studies of Immunology. *Id.* Dr. Bellanti testified that his current status is *emeritus*. He currently teaches, does "a little research," and sees patients with complex immunological problems on referral one day each week. Tr. 73. He has published considerable medical articles, as well as several chapters and entire textbooks. Pet. Ex. 96 at 12-46. He is the sole author of a textbook on immunology. One chapter from his textbook was filed in this case.[7] Upon review of the transcript, I recognize that petitioner did not move to admit Dr. Bellanti in a particular field. However, his testimony was centered on the field of immunology. Respondent did not challenge his qualifications in that field.

[8] Dr. Wiznitzer is board-certified in pediatrics, psychiatry and neurology with a special qualification in child neurology, neurodevelopmental disabilities, and medical examination. Resp. Ex. C at 6. Dr. Wiznitzer received his medical degree from Northwestern University in 1977. *Id.* at 1. He then spent three years as a resident in pediatrics at what is now named Cincinnati Children's Hospital in Ohio, then one year as a fellow at the Cincinnati Center for Developmental Disorders, and then three years as a fellow in pediatric neurology at the Children's Hospital of Philadelphia, Pennsylvania. *Id.* He then spent two years as a NIH-sponsored fellow in higher cortical functions at Albert Einstein College of Medicine in the Bronx, New York. *Id.* In 1986, he was hired by Case Western Reserve University, where he is now a professor of neurology and pediatrics. *Id.* at 2-3. He is also a child neurologist seeing both outpatients and inpatients at Rainbow Babies and Children's Hospital in Cleveland, Ohio. *Id.* at 2-3; Tr. 116. Dr. Wiznitzer testified that currently eighty-five percent of his job is direct patient care. Tr. 118. He has diagnosed and treated children with febrile seizures, epilepsy, and autoimmune encephalopathies. Tr. 120. I granted respondent's unopposed motion to admit Dr. Wiznitzer as an expert in pediatric neurology. Tr. 122.

[9] Dr. Lobo unfortunately passed away the year after the hearing in this case. He was board-certified in allergy and immunology. Resp. Ex. T at 1. He received his medical degree from the Yale University School of Medicine in

Exs. S, EE. While the case proceeded on a litigation track, the parties discussed settlement and reached a tentative settlement agreement. Ultimately, the tentative agreement did not receive final approval from respondent. On October 2-3, 2017, an entitlement hearing took place during which the four experts testified. *See* Transcript ("Tr.") (ECF Nos. 118, 120). The parties have filed their respective post-hearing briefs. The matter is now ripe for adjudication.

II. Legal Standard[10]

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Human Servs.*, 35 Fed. Cl. 1, 7 (1996) (quoting H.R. No. 908 at 3, *reprinted in* 1986 U.S.C.C.A.N. at 6287, 6344).

A petitioner bears the burden of establishing his or her entitlement to compensation from the Vaccine Program. There are two avenues to compensation. The first requires the petitioner to demonstrate a Table injury but that is not alleged in the present case.[11] The second avenue requires the petitioner to prove that a vaccine listed on the Vaccine Table was the cause-in-fact of the injury.

To satisfy the burden of proving causation-in-fact, petitioner must "show by preponderant evidence that the vaccination brought about the injury by providing 1) a medical theory connecting the vaccination and injury; 2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and 3) a showing of proximate temporal relationship between vaccination and injury." *Althen v. Sec'y of Health & Human Servs.*, 418 F. 3d 1274, 1278 (Fed. Cir. 2005). The petitioner must establish each *Althen* prong by the preponderance of the evidence. *Caves v. Sec'y of Health & Human Servs.,* 100 Fed. Cl. 119, 132 (2011), *aff. per curiam,* 463 Fed. Appx. 932 (Fed. Cir. 2012).

1992. *Id.* He remained at Yale for the remainder of his life. He spent the first two years as a resident in internal medicine, then four years as a post-doctoral fellow in the department of pediatrics, section of allergy and clinical immunology. *Id.* In 1998, he was appointed as an instructor at Yale. *Id.*; Tr. 235. He was most recently a clinical instructor in the department of pediatrics, section of allergy and clinical immunology. Resp. Ex. T at 1. He also maintained a clinical practice. Approximately half of his patients were children and half were adults. Tr. 236. He treated conditions including immune deficiency, allergy, drug hypersensitivity, and autoinflammatory diseases. Tr. 236. Dr. Lobo conducted original research on immunology, including on delay-type hypersensitivity reactions and the timeframe and kinetics of antibody formation. Tr. 237. Tr. 237. While the other three experts are all established in the Vaccine Program, for Dr. Lobo, this was the second Vaccine Program case in which he had submitted a report and the first case in which he had testified. Tr. 238. Upon respondent's unopposed motion, I admitted Dr. Lobo as an expert in immunology.

[10] Decisions of special masters and the U.S. Court of Federal Claims (some of which are referenced in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd*, 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

[11] *See infra* note 4.

The preponderance of the evidence standard requires a petitioner to demonstrate that it is "more likely than not" that the vaccine caused her injury. *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.,* 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [a] but for cause of the injury but also a substantial factor in bringing about the injury." *Moberly,* 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs.,* 135 F.3d 1344, 1352-53 (Fed. Cir. 1999); *Pafford v. Sec'y of Health and Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). Causation is determined on a case-by-case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). A fact-finder may rely upon "circumstantial evidence" which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Althen,* 418 F. 3d at 1280.

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires petitioners to present expert testimony in support of his or her claim. *Lampe v. Sec'y of Health & Human Servs.,* 219 F.3d 1357, 1361 (Fed. Cir. 2000). Expert testimony in the Vaccine Program is usually evaluated according to the factors set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo,* 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Human Servs.,* 195 F.3d 1302, 1316 (Fed. Cir. 1999). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly* at 1324. The *Daubert* factors are used in *weighing* the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.,* 94 Fed. Cl. 53, 66-67 (2010). Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs*., 219 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Human Servs.,* 219 F.3d 1357, 1362 (Fed. Cir. 2000).

Once a petitioner has proven causation by preponderant evidence, the burden shifts to respondent to show by a preponderance of the evidence that the injury is due to factors unrelated to the administration of the vaccine. *Deribeaux v. Sec'y of Health & Human Servs.,* 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing § 13(a)(1)(B)). Respondent has the burden of demonstrating that "a factor unrelated to the vaccination is the more likely or principal cause of injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury. If the evidence or alternative cause is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded." *Knudsen,* 35 F.3d at 551.

II. Summary of Medical Records

1. M.S.M.'s Medical History Before the March 11, 2013 Vaccinations

M.S.M. was born at term in early September 2012. Her Apgar scores, neonatal evaluation, and physical examination were all normal. Pet. Exs. 8, 9. Primary care was established initially at the Laurel Children's Clinic, where at one month old, M.S.M. received the first hepatitis B vaccination. At two months old, she received the first DTaP, Hib, IPV, PCV, and rotavirus vaccinations. At each visit, she was recorded to have normal tone and motor development. She followed to midline. She lifted her head while lying on her stomach. Pet. Ex. 11 at 5-8.

Primary care was then transferred to Dr. Carlos A. Cruz, who saw her twice in December 2012 for a cough and pulling on one ear. He noted that her left eye seemed smaller than the right and she exhibited strabismus.[12] The physical exams were otherwise normal. Pet. Ex. 1 at 1-2.

On January 8, 2013, at four months old, M.S.M. received the second DTaP, Hib, IPV, PCV, Hep B, and rotavirus vaccinations at Dr. Cruz's office. She was seen by another physician, Dr. Villagra, who recorded strabismus and an otherwise normal physical examination. Pet. Ex. 1 at 3. On January 15, 2013, Dr. Cruz saw M.S.M. for fussiness and constipation, which he assessed to be functional. He recorded that M.S.M. had cradle cap. He recorded no history of fever or present fever or any other issues. Pet. Ex. 1 at 4.

On March 11, 2013 at approximately 11:30 a.m.[13] Dr. Cruz saw M.S.M. for her six-month well visit. He recorded no reactions to prior vaccinations. He observed no strabismus. On physical examination, he recorded "generalized hypotonia."[14] This is the first record noting hypotonia. However, everything else in the record appears normal and inconsistent with hypotonia or any other developmental delay. Dr. Cruz wrote "NL [normal] milestones." He also wrote that "neuro/ reflexes/ tone" were within normal limits. Under "[d]evelopmental surveillance (observed or reported)," he wrote that M.S.M. could transfer toy hand to hand, feed self crackers, work for toy out of reach, say dada or mama non-specific, turn to voice, and imitate speech sounds. She could sit alone (without support), stand holding on, bear weight on legs, and had no head lag when pulled to sitting. Pet. Ex. 1 at 5 (well visit record); *see also id.* at 21 ("Denver II" graph indicating that she met many developmental milestones for her age of six

[12] Strabismus is "an eye condition in which the visual axes cannot be directed at the same point of fixation under normal conditions of seeing." *Dorland's Illustrated Medical Dictionary* 32nd Ed. (2012) (hereinafter "*Dorland's*") at 1778.

[13] Dr. Cruz's contemporaneous medical record does not indicate the time of the visit. However, four days later he completed a VAERS report on which he states that the vaccinations were given on March 11, 2013 at 11:30 a.m. Pet. Ex. 1 at 31.

[14] Hypotonia is "a condition of diminished tone of the skeletal muscles, so that they have diminished resistance to passive stretching and are flaccid." *Dorland's* at 907 (picturing a child displaying "hypotonia with severe head lag and failure of limbs to flex to counter the upward traction").

months). M.S.M. received her third DTaP, Hib, IPV, PCV, Hep B, and rotavirus vaccinations. Pet. Ex. 1 at 5, 23.

2. M.S.M.'s Medical History After the March 11, 2013 Vaccinations

On March 12, 2013 at approximately 3:00 a.m., M.S.M. awoke and began staring, drooling, and shaking. The parents drove her to the emergency room at Holy Cross Hospital in Silver Spring, Maryland, which took at least 15 minutes.[15] She presented at approximately 3:30 a.m. She was admitted at 3:49 a.m. The parents' preferred language was Spanish and they needed an interpreter. The emergency room records provide that M.S.M. was experiencing a right-sided tonic-clonic seizure. That seizure was also described as "focal." It constituted "status epilepticus." Her rectal temperature was 102.8 degrees Fahrenheit. Within 5 minutes of arrival, she received rectal acetaminophen (an analgesic used to reduce fever) and lorazepam (a treatment for seizures), after which the seizure activity stopped. Thus, the seizure lasted at least 30 minutes. Pet. Ex. 10 at 46-49.

Labwork showed a white blood cell ("WBC") count of 34.4 K/uL (above the reference range of 5.0 – 15.5 K/uL). Pet. Ex. 10 at 51. A resident suggested the elevated WBC could be "elevated due to stress of seizure itself but should be continued to be monitored." *Id.* at 18. M.S.M. was given one dose of ceftriaxone (an antibiotic). *Id.* at 39.

At approximately 6:00 a.m., a pediatrician, Dr. Wiersma, recorded that M.S.M. "remained sleepy." The parents reported that M.S.M. had been meeting developmental milestones and was babbling and transferring objects, but "was not yet sitting unassisted." Pet. Ex. 10 at 16-17.

At approximately 8:00 a.m., another pediatrician, Dr. Cuzzi, saw M.S.M. The parents described an earlier incident. Namely, the night before at approximately 10:00 p.m., M.S.M. had "1 minute staring fixed forward, mouth closed, body tense, no clonic activity. [M.S.M.] fell asleep directly after this event." Pet. Ex. 10 at 19. This was before the prolonged seizure which led to the hospitalization at approximately 3:30 a.m. Dr. Cuzzi noted that after the prolonged seizure, M.S.M. was "postictal." *Id.* at 19. At 8:00 a.m., Dr. Cuzzi observed M.S.M. "sleeping initially, fairly easy to awaken but sleepy, focuses on examiners, smiles, follows 180 degrees, reaches but did not grasp on this exam, does not roll over, pushes chest up and head up 90 degrees, small head lag when pulled to sit, when held sitting head is off-center/ lopsided as if unable to hold central firm (different from baseline per dad)." *Id.* Dr. Cuzzi's assessment was complex febrile seizures and "delayed gross motor milestones." *Id.* at 21.

At 11:30 a.m., a medical student called M.S.M.'s primary care provider Dr. Cruz, who reported that M.S.M. did not have "any developmental delay at her 4 month or 6 month visits." Pet. Ex. 10 at 30.

[15] The family's home address is listed on the hospital face sheet. Pet. Ex. 10 at 1. By my calculation using www maps.google.com, the home is at least 4.8 miles and at least 15 minutes driving time to the hospital (depending on the route taken).

Also on March 12, 2013, a pediatrician at the hospital, Dr. Rochester, recorded that a neurologist had recommended short-term close observation, diazepam (another treatment for seizures) at discharge, and a neurology follow up in 4-6 weeks. *Id.* at 21. Dr. Rochester also examined M.S.M. at 5:30 p.m. She was awake and alert. "Neuro exam was significant for gross motor delay (doesn't reach for toys, unable to sit without support, head bobbing noted when in sitting position) – all present at baseline per parents." *Id.* Dr. Rochester's assessment was: "6 mo s/p complex febrile seizure with no source of fever on exam, now well-appearing and back to baseline per parents. Fever was likely secondary to immunizations. Exam and hx are notable for motor delay (fine and gross.)" *Id.* at 22.

On March 13, 2013, repeat lab work showed a decreased WBC of 22.7 K/uL. *Id.* at 6. Additionally, M.S.M. did not have any further fevers, did not appear meningitic, and "returned to baseline mental status." Pet. Ex. 10 at 5. Therefore, she was discharged on March 14 at approximately 10:00 a.m. The discharge summary, signed by Dr. Wiersma, instructed that if M.S.M. experienced a further seizure, she should take Diastat 2.5 mg (provided) and return to the emergency room. *Id.* at 4. She needed to follow up with her primary care provider Dr. Cruz the next day and a neurologist on April 22, 2013. *Id.* Dr. Wiersma also wrote that M.S.M. had been found "mildly developmentally delayed by Denver assessment (failed both gross and fine motor)." *Id.* at 5. Dr. Wiersma recommended following up on this issue, possibly by "refer[r]al [sic] to infants and toddlers." *Id.* at 7.

On March 15, 2013, Dr. Cruz saw M.S.M for follow up. He again recorded normal milestones, but generalized hypotonia. Pet. Ex. 1 at 6. Subsequently, on April 12, Dr. Cruz filed a VAERS report. *Id.* at 31.

On April 22, 2013, Dr. Reese, a neurologist affiliated with Children's National Medical Center ("CNMC"), conducted an initial evaluation. Dr. Reese recorded that the mother recalled that during the March 11 seizure involved both arms and both legs, which would be described as generalized and non-focal. This would be the "best case scenario." But in contrast, the hospital records only recorded right-sided seizure activity, which would be focal. Dr. Reese did not prescribe any medication at this visit. He recommended an MRI without contrast and an EEG to exclude underlying etiologies for focal seizures. Pet. Ex. 2 at 31-33.

On April 23, 2013, M.S.M. suffered another seizure. Her mother reported that the previous evening, M.S.M. "felt hot." The mother did not take M.S.M.'s temperature but gave ibuprofen. Pet. Ex. 10 at 178. The next morning, M.S.M. was asleep. She suddenly screamed, went limp, and then all of her limbs shook. She stopped breathing, drooled, and vomited. She did not turn colors. The episode lasted 2-3 minutes. She was transported by ambulance. In the emergency room, her temperature was 101.2 degrees Fahrenheit. She was "alert and smiling during triage." There was "no postictal phase." An emergency room physician communicated with Dr. Reese, and then discharged M.S.M. home. Pet. Ex. 10 at 164-91.

On May 17, 2013, Dr. Reese met again with M.S.M. and her mother, with assistance from a Spanish-speaking interpreter on the phone. He noted that the MRI (performed on May 2, 2013) showed no brain abnormality, but the brain's internal architecture could not be seen due to M.S.M.'s young age. Dr. Reese explained the difference between an MRI and EEG and why

both should be done. He did not prescribe any medication. Pet. Ex. 2 at 36-38; *see also id.* at 34-35 (MRI report).

On June 1, 2013, Dr. Cruz conducted a routine 9-month old visit. He again observed that M.S.M. had generalized hypotonia. She had new decreased mobility of the left arm, was unable to roll over, and did not sit unsupported. Dr. Cruz recorded that she was developmentally delayed by Denver screening. Pet. Ex. 1 at 9. On June 5, M.S.M. was referred to the Maryland Infants & Toddlers Program. An evaluation on July 17, 2013 found that she was experiencing at least 25% developmental delay in fine and gross motor skills. Pet. Ex. 12 at 1-2.

On July 3, 2013, the EEG requested by Dr. Reese was performed. The impression was: "Abnormal routine video EEG capturing wakefulness through stage 1 sleep due to the presence of frequent multifocal and likely secondarily generalized discharges during drowsiness and sleep. This would suggest lowered seizure threshold." Pet. Ex. 2 at 39-40.

On August 2, 2013, Dr. Reese saw M.S.M. again. He noted that M.S.M. had begun physical therapy twice a month. Dr. Reese agreed that the EEG and the MRI suggested that M.S.M. was "at an increase[d] risk for recurrent seizures, but we cannot say that risk is high enough to warrant medication at this time." He did not suggest any further workup. The mother asked, on behalf of the primary care provider Dr. Cruz, whether M.S.M. should receive further vaccines. Dr. Reese indicated: "Febrile seizure is not a contraindication for vaccines. [M.S.M.] did not have any findings on her MRI suggestive of metabolic disease." Pet. Ex. 2 at 41-43.

On August 22, 2013, Dr. Cruz's office recorded that "per Dr. Reese, is okay for [M.S.M.] to receive vaccinations." Pet. Ex. 1 at 19. Subsequently, M.S.M. received MMR and varicella vaccinations on September 10, 2013 and a hepatitis A vaccination on October 10, 2013 without incident. *Id.* at 11-12, 23.

On October 22, 2013, Dr. Reese saw M.S.M. because her therapists were concerned that she was having seizures. Dr. Reese observed several such episodes during the visit. "[M.S.M.'s] head would fall to the left side and then roll forward. It happened more slowly than the atonic seizures [Dr. Reese] was accustomed to seeing." Pet. Ex. 2 at 46-48.

At Dr. Reese's recommendation, on November 21, 2013, a video EEG was performed. The impression was abnormal due to multifocal epileptiform discharges, predominantly in the bilateral occipital regions. In addition, there were bursts of bi-occipital/ generalized epileptiform discharges, sometimes associated with relatively subtle leg myoclonus or subtle head drops/ eye fluttering. This supported a significantly lowered seizure threshold. A clinical diagnosis of Dravet syndrome was suggested. Pet. Ex. 2 at 50-51.

At the next visit on December 2, 2013, Dr. Reese recorded that the head drops seemed to be increasing in frequency. He observed two such episodes. He found her EEG and clinical presentation were suggestive of Dravet syndrome. "To confirm the diagnosis of Dravet," he recommended testing for the SCN1A gene. "If this test comes back positive, it would have implications about which seizure medicines to use or avoid." Pet. Ex. 2 at 54-55. He also wrote the first prescription for M.S.M. to take the seizure medication levetiracetam. Pet. Ex. 7 at 1; Pet. Ex. 13 at 1.

At a December 12, 2013 follow-up, Dr. Cruz recorded that M.S.M. had been prescribed levetiracetam. "According to parents when she takes meds she doesn't have seizures, but sometimes she refuses to take the medications [and has?] seizure activity." Dr. Cruz encouraged administering the medication in different ways. He recorded that M.S.M. was able to support weight, walk with assistance, and sit unsupported but she had low tone. Pet. Ex. 1 at 13.

On December 20, 2013, Dr. Reese recorded that the physical therapist had observed "over 15 head drops" during therapy that day and raised the possibility of a helmet. Additionally, the mother had "expressed hesitancy to [the physical therapist] about using medication." Pet. Ex. 2 at 53.

On December 26, 2013, Dr. Cruz saw M.S.M. for another routine visit. His physical examination observed generalized hypotonia, but able to sit unsupported. He noted that a developmental screening showed gross motor delay and speech delay, but she was already on PT/ OT/ speech therapy three times per week. Pet. Ex. 1 at 14. Dr. Cruz administered the fourth DTaP, Hib, and PCV vaccinations. *Id.* at 23.[16] The previous round of these vaccines had been given March 11, 2013, less than 24 hours before her first status epilepticus.

3. M.S.M.'s Medical History Following the Repeat Vaccinations on December 26, 2013

On December 27, 2013 in the early morning, M.S.M. "had a spontaneous seizure that lasted for 5 minutes." The parents called an ambulance which was dispatched at 4:56 a.m., arrived at 5:02 a.m., reached Holy Cross Hospital at 5:23 a.m., and transferred care at 5:32 a.m. Pet. Ex. 10 at 254-56. At 5:50 a.m., it was recorded that M.S.M. was "actively seizing… with deviated eyes to the left and generalized twitching" upon arrival to the emergency room. At 5:57 a.m., it was recorded that the first two attempts to place an intravenous (IV) line were unsuccessful. At 6:00 a.m., the seizure activity stopped. She was crying and responsive to pain with the IV line attempts. Her pediatric Glasgow coma scale was 10. Pet. Ex. 10 at 235-79. Thus, it is likely that this seizure lasted at least 30 minutes.

At 6:06 a.m., the IV line was established. At 6:26 a.m., levetiracetam was infusing through the IV line. Her rectal temperature was 102.2 degrees Fahrenheit. Pet. Ex. 10 at 235-40.

The attending physician recorded that M.S.M. had "missed 2 doses [of levetiracetam] because pharmacy did not have refill." Pet. Ex. 10 at 251. Labwork taken prior to the infusion at the hospital showed levetiracetam was at less than 1.0 mcg/ mL (below a therapeutic "trough" of 4.9 – 37.1 mcg/ mL). *Id.* at 261. The hospitalization records do not mention the vaccines that M.S.M. had received from her primary care provider the previous day. Later that morning, M.S.M. was discharged with diazepam to last one day, levetiracetam for three days, and instructions to refill the levetiracetam prescription. *Id.* at 246.

[16] The contemporaneous record does not indicate the time of the visit or the time the vaccines were given.

Dr. Reese had referred M.S.M. to a geneticist, Dr. Lewanda, to "rule out Dravet syndrome." Pet. Ex. 2 at 61. At the initial genetics visit on January 3, 2014, Dr. Lewanda reviewed M.S.M.'s history and EEG findings and agreed with the concern. She wrote:

> [Dravet syndrome] is an early-onset epileptic encephalopathy which is characterized by generalized tonic, clonic, and tonic-clonic seizures that are initially induced by fever and begin in the first year of life. They are often refractory to treatment. Later, these seizure types can change and include other forms such as myoclonic, absence, or partial seizures. Development typically stagnates around the second year of life, and there can be subsequent mental decline and other neurologic manifestations.

Dr. Lewanda agreed that testing for the SCN1A gene was important and the results could inform M.S.M.'s treatment plan. She planned to seek approval from the health insurance provider. *Id.* at 61-63.

On January 6, 2014, Dr. Reese saw M.S.M. again. He briefly noted that in December 2013, one day after receiving DTaP, Hib, and PCV vaccines, M.S.M. had an "event" at home which prompted the mother to call 911 and have M.S.M. "taken to Holy Cross and then discharged home." Dr. Reese does not discuss the active seizing at the hospital. "Other than that, [M.S.M] ha[d] been doing well." She was compliant with levetiracetam, with "significant improvement with her seizures" and "0 to a few seizures per day." Pet. Ex. 2 at 68-71.

M.S.M. underwent audiology tests regarding her speech and language development in January and again in March 2014. Pet. Ex. 2 at 25-27, 72-77. She continued with her therapists. Pet. Ex. 12 at 13-47. Pediatric care remained with Dr. Cruz for much of 2014. Pet. Ex. 1 at 15-17. But in September 2014, pediatric care was transferred to a Dr. Hashim. Pet. Ex. 3 at 1-7; Pet. Ex. 85 at 5-7.

On May 9, 2014, at approximately 3:00 p.m., M.S.M. presented at Holy Cross Hospital. The mother reported that the previous evening, M.S.M. had developed hives (also described as a rash) and a low-grade fever. She was taking ibuprofen. At the hospital, M.S.M.'s temperature was 100.0 degrees Fahrenheit. The impression was a viral syndrome and hives. She was sent home. Pet. Ex. 10 at 199-232.

On May 11, 2014, the parents took M.S.M. to urgent care because the hives were still present. The assessment was an allergic reaction. Her temperature was 97.6 degrees Fahrenheit. Pet. Ex. 6 at 1-3.

Neurology care continued with Dr. Reese. His opinion was that the EEGs and clinical presentation were most consistent with Dravet syndrome. In March 2014, he prescribed M.S.M. a soft helmet. He adjusted levetiracetam several times. Increasing the prescription somewhat improved but did not fully control her seizure activity. Dr. Reese also recorded that the mother had begun giving M.S.M. melatonin to help her sleep, which was associated with decreased seizures. Pet. Ex. 2 at 15-23, 79-93; Pet. Ex. 14 at 1-16.

On January 30, 2015, M.S.M.'s parents sought a second neurology opinion from Dr. Yuval Shafrir at Sinai Hospital in Baltimore, Maryland. After reviewing the records and conducting his own evaluation, Dr. Shafrir's impression was that M.S.M. had a "severe early epileptic encephalopathy, which was triggered by her DTaP vaccination." He considered that Dravet Syndrome was "definitely high on the list." He opined that levetiracetam alone did not seem to help M.S.M. He recommended a different anti-seizure medication, divalproex sodium. If the diagnosis of Dravet syndrome was confirmed, he recommended adding stiripentol, a supplemental anti-convulsant treatment specifically for Dravet syndrome which is not adequately controlled by other drugs.

Dr. Shafrir explained that if M.S.M. was transferred to his care, he would like to see her 5-6 times per year. Additionally, he would require another video EEG and that any emergency care take place at his hospital (which was some distance away from M.S.M.'s home). Pet. Ex. 85 at 25-38 (Dr. Shafrir's letter to primary care provider Dr. Hashim); Tr. 13-14.[17] Thus, the parents decided to continue with their established neurologist, Dr. Reese. Pet. Ex. 16.

After the parties stipulated that it would be a litigation cost incurred by the Vaccine Program, Dr. Shafrir ordered an SCN1A genetic sequencing test. In April 2015, a report concluded: "No sequence variants were detected in SCN1A. This result does not support a diagnosis of SCN1A-related seizure disorder." However, it further provided: "It cannot be excluded that pathogenic variants in SCN1A were missed due to limitations inherent to the sequence analysis method used here. In addition, presence of SCN1A-related seizure disorder due to a different genetic cause can also not be ruled out." Pet. Ex. 17.

In October 2015, a comprehensive epilepsy panel/ sequencing and deletion/ duplication analysis of 70 genes was obtained from a company called GeneDx. The report provides that M.S.M. was "heterozygous for a variant of uncertain significance" in the PNKP gene. Pathogenic variants in the PNKP gene have been associated with autosomal recessive microcephaly, seizures, and developmental delay (MCSV) as well as with polyneuropathy. However, it was unclear whether the single variant found in M.S.M. was pathogenic or benign. The report also noted: "A second pathogenic variant, as expected for an autosomal recessive disorder, was not detected… The finding of a single missense variant makes the molecular diagnosis inconclusive, and clinical findings should also be considered in the diagnosis of [M.S.M.]." Importantly, once again, no mutations/ variants in the SCN1A gene were found. The report authors suggested genetic counseling and whole exome sequencing. Pet. Ex. 63. However, there are no records of that occurring.

[17] I note that by this point, petitioner had retained the Shoemaker firm, who referred her to Dr. Shafrir. While the initial consultation was – at least in part – to possibly transfer M.S.M.'s neurologic care to Dr. Shafrir, petitioner and the Shoemaker firm also retained Dr. Shafrir as an expert witness. *See, e.g.*, Pet. Ex. 18 (Dr. Shafrir's first expert report dated May 30, 2015, which largely resembles his letter to the primary care provider Dr. Hashim). Dr. Shafrir's expert opinion is addressed in further detail below.

III. Analysis[18]

1. *Althen* Prong One: Petitioner's Theory

Under *Althen* prong one, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). It must only be "legally probable, not medically or scientifically certain." *Id.* at 549. However, the theory still must be based on a "sound and reliable medical or scientific explanation." *Knudsen* at 548. The Federal Circuit explained in *Althen* that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen*, 418 F.3d at 1280 (emphasis added).

A. Innate Immune Response

Petitioner and her experts opined that the vaccines at issue activate an innate immune response which includes the rapid generation of pro-inflammatory cytokines, which can cause fever and status epilepticus resulting in encephalopathy, which can cause developmental delay and further seizure activity.

Petitioner's first expert retained in this case was the neurologist, Dr. Shafrir. He opined that certain individuals are uniquely susceptible to autoimmune diseases. The exact pathway is not fully understood. Pet. Ex. 18 at 24-25; see also Pet. Ex. 92 at 1. Later in the case (after a tentative settlement was not approved by respondent's counsel), respondent retained an immunologist, Dr. Lobo, which prompted petitioner to retain her own immunologist, Dr. Bellanti. Dr. Bellanti concurred that some individuals react badly to a vaccine while the overwhelming majority of individuals do not. Dr. Bellanti opined that perhaps these individuals have an unusual genetic or immune component which "render[s] a given individual more susceptible to having an adverse reaction to a vaccine or an infectious process." Pet. Ex. 95 at 2. As noted elsewhere in this opinion, M.S.M. was not found to have any known pathogenic genetic mutation.

From the start of the case, petitioner's first expert Dr. Shafrir offered various opinions, including that vaccines can activate an *innate* immune response involving increased production

[18] While I have reviewed all of the medical records, expert opinions, and medical literature submitted in this case, I discuss only those which are most relevant to my determination and/ or are central to petitioner's case. *Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) (internal citation omitted) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision"); *see also Paterek v. Sec'y of Health & Human Servs.*, 527 Fed. App'x 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to – and likely undermines – the conclusion that it was not considered").

of pro-inflammatory cytokines. Pet. Ex. 64 at 4.[19] He opined that the vaccines at issue can activate an innate immune response occurring within zero to 72 hours. The response involves pro-inflammatory cytokines which cross the blood-brain barrier into the brain, where they activate the hypothalamus to produce fever. Tr. 34-35. Dr. Shafrir opined that fever is a precipitant for seizures, particularly in patients who have an underlying susceptibility. Tr. 34-36.

After petitioner retained Dr. Bellanti, he expanded on this mechanism of injury. Dr. Bellanti opined that the innate arm of the immune system is present at birth. It can respond upon the very first exposure to a foreign pathogen. The response is non-specific but rapid. Upon repeat exposure to a foreign pathogen, the innate immune response still occurs first and is followed by the adaptive immune response.

A fetus receives a certain amount of IgG antibodies from his or her mother. The IgG antibodies received from the mother only last for a transient period of time. Then, the fetus starts to make his or her own gamma globulins in a sequential fashion: IgM first followed by IgG, followed by IgA and IgE. During the first year of life, the adaptive immune response is not fully developed but it is there. Pet. Ex. 95 at 4-7; Pet. Ex. 116 at 9-25; Tr. 86. Dr. Bellanti opined that past research of immune dysfunction and injury has focused on the adaptive arm but recently, increased attention is being paid to the innate arm. Pet. Ex. 95 at 4-5; Pet. Ex. 116 at 29-31.[20]

Dr. Bellanti opined that the innate response involves the production of pro-inflammatory cytokines such as interleukin 1 ("IL-1") which stimulates the hypothalamus which causes fever. Fever, on its own, is a normal immune response and is common following vaccination, affecting up to ten percent of children vaccinated in the United States.

Dr. Bellanti stated that the immune system depends on "homeostasis" or "equilibrium". When the immune system functions properly, the pro-inflammatory cytokines are produced, perform their role, and then are balanced out by anti-inflammatory cytokines. In rare cases, there is immunologic disequilibrium where the pro-inflammatory cytokines are not balanced out. Dr. This causes not only cause normal fever, but also trigger epileptogenic activity in the brain resulting in seizure. Dr. Bellanti testified that fever with *seizure activity* occurs in a smaller percentage of children vaccinated in the United States. Tr. 76-77, 80-83, 114-15. He also testified that the risk of febrile seizure increases with the number of childhood vaccines given. He found significant that on March 11, 2013, M.S.M. received over twenty antigens (within the DTaP, IPV, Hib, Hep B, Prevnar, and rotavirus vaccines), which was "a real cocktail of vaccines that she hadn't received previously." Tr. 84.

[19] Citing Matin N. et al., *Epilepsy and Innate Immune System: A Possible Immunogenic Predisposition and Related Therapeutic Implications*, 11 Human Vaccines & Immunotherapeutics 2021-29 (2015) [Pet. Ex. 70]; Iori V, et al., *Modulation of Neuronal Excitability by Immune Mediators in Epilepsy*, 26 Curr. Opin. Pharmacol. 118-23 (2016) [Pet. Ex. 71].

[20] Citing Koenig H.C. et al., *Application of the Immunological Disease Continuum to Study Autoimmune and Other Inflammatory Events after Vaccination*, 29 Vaccine 913-19 (2011) [Pet. Ex. 97]; Descotes J. & G. Choquet-Kastylevsky, *Gell and Coombs's Classification: Is It Still Valid?*, 158 Toxicology 43-49 (2001) [Pet. Ex.110].

Dr. Bellanti opined that the dysfunction in the innate immune system described above can be caused by the vaccines in this case. He submitted two studies for the proposition that whole-cell pertussis toxin can activate IL-1. Tr. 82.[21] Dr. Shafrir also focused on pertussis. He cited the United Kingdom's National Childhood Encephalopathy Study (NCES) which reported that compared to a control group of unvaccinated children, children who received the diphtheria, tetanus, whole-cell pertussis toxin (DTP) vaccine had an increased incidence of serious neurological illness (including encephalopathy, convulsions, and coma) within 72 hours.[22] No significant association was found between DT (without any pertussis component) and serious neurological illness. *Id.* Dr. Shafrir characterized this study as "a basis for the compensation for DTP vaccination." Pet. Ex. 18 at 20; Tr. 25-27. Respondent's experts Dr. Wiznitzer and Dr. Lobo objected to references to the whole cell pertussis toxin. They acknowledged that whole cell pertussis toxin was associated with these adverse events, but that prompted development of vaccines with the acellular pertussis toxoid which achieves the desired immunological effect but *decreases* the incidence of adverse events. *See, e.g.*, Resp. Ex. B at 11 and Tr. 184-85 (Dr. Wiznitzer); Tr. 261 (Dr. Lobo).

Dr. Shafrir also cited a Polish epidemiological study[23] which found no statistically significant difference in the frequency of encephalopathy following DTP and DTaP vaccine. Pet. Ex. 18 at 20. Those authors wrote: "The data presented here confirm general knowledge of higher incidence of systemic adverse effects after whole cell pertussis preparations than acellular ones… The higher rate of seizures could be attributed mostly to higher rate of high fever after whole cell preparations." Pet. Ex. 32 at 6.[24] Further: "In *most* instances, acellular vaccine is less reactogenic and more comfortable for children and their custodians. *But severe and serious reactions are very rare after either type of preparation, and even if they are more frequent after whole-cell vaccines, the rates were not significant*." *Id.* (emphasis added). This Polish study has previously been accepted for the proposition that acellular pertussis toxoid vaccine still carries risk for neurological injury including encephalopathy. *See, e.g.*, *Johnson v. Sec'y of Health & Human Servs.*, No. 07-138V, 2010 WL 3291932, *15 (Fed. Cl. Spec. Mstr. July 30, 2010) (accepting Dr. Shafrir's proffer of the Polish study, over Dr. Wiznitzer's opposition, and concluding that DTaP and other vaccines caused febrile seizure and encephalopathy); *see also Romero v. Sec'y of Health & Human Servs.*, No. 07-671V, 2010 WL 2766761, *15 (Fed. Cl. Spec. Mstr. June 22, 2010) (citing other literature for the conclusion that DTaP reduces but does

[21] Dumas A. et al., *The Inflammasome Pyrin Contributes to Pertussis Toxin-Induced IL-1β Synthesis, Neutrophil Intravascular Crawling and Autoimmune Encephalomyelitis*, 10 PLoS Pathog. E1004150 (2014) [Pet. Ex. 111]; Loscher C. et al., *Proinflammatory Cytokines in the Adverse Systemic and Neurologic Effects Associated with Parenteral Injection of a Whole-Cell Pertussis Vaccine*, 856 Annals of the New York Academy of Sciences 274-77 (2006) [Pet. Ex. 118].

[22] Miller, D.L. et al., *Pertussis Immunization and Serious Acute Neurological Illness in Children*, 282 British Med. Journal 1595-99 (1981) (hereinafter, "NCES") [Pet. Ex. 31].

[23] Zielinski A. & M. Rosinska, *Comparison of Adverse Effects Following Immunization with Vaccine Containing Whole-Cell vs. Acellular Pertussis*, 62 Przegl. Epidemiol. 589-96 (2008) [Pet. Ex. 32].

[24] The study results section seems to define "high fever" as fever greater than 39 degrees Celsius (102.2 degrees Fahrenheit). Pet. Ex. 32 at 4, 5.

not eliminate the incidence of uncommon adverse events such as seizures).[25] Dr. Bellanti also opined that the DTaP vaccine "eliminates a lot," but not "completely" all adverse events. Tr. 84.

Respondent's experts did not respond to the Polish study's findings of adverse events following DTaP vaccines.[26] Neither did they submit any literature on neurological injury following the pertussis toxin compared to the toxoid.

Upon consideration of the evidence, I accept the proposition that acellular pertussis toxoid still carries some risk for adverse reactions in a susceptible individual. This may occur because the vaccine activates pro-inflammatory cytokines which are not appropriately counter-balanced by anti-inflammatory cytokines, which results in excess neuronal excitation and seizures. It is also noted that petitioner's experts did not opine only about pertussis. For example, they also referenced the number of vaccine antigens that were administered to M.S.M. at once and the alum adjuvant used in several of the vaccines. *See, e.g.*, Pet. Ex. 95 at 3, 6, citing Koenig [Pet. Ex. 97]. I also find these facts to be probative to the degree of the immune response.

Respondent's experts raised many objections in this case, but they basically agreed with the innate immune response theory described above. On cross-examination, Dr. Lobo agreed that "vaccines increase cytokine circulation… cytokines travel to the brain, they cross the blood-brain barrier… and go to the hypothalamus… and cause fevers within minutes to hours." Tr. 278-79. Dr. Lobo also agreed that fever can induce seizure. Pet. Ex. EE at 3-4. Dr. Wiznitzer agreed that the vaccines can cause fever and status epilepticus, and in fact they did in M.S.M. *See, e.g.*, Tr. 135, 142-44, 227.

Following from that proposition, Dr. Shafrir, a well-qualified neurologist and epileptologist, opined that status epilepticus can lower an individual's threshold for further seizures. Pet. Ex. 18 at 23, 26. In his reports, Dr. Wiznitzer did not respond on this point; instead, he pivoted to other arguments. First, he argued that there was no evidence that status epilepticus lowered M.S.M.'s threshold for further seizures. Resp. Ex. B at 9-10, 12. This is more appropriately discussed below under *Althen* prong two regarding the sequence of cause and effect in M.S.M.'s case. As discussed below, I conclude that it is more likely than not that the status epilepticus *did* damage M.S.M.'s brain and lower her threshold for further seizure activity. Second, Dr. Wiznitzer opined that M.S.M. may have a "genetic mutation in an ion channel different than SCN1A or another brain protein," which explained all of her seizure activity

[25] Additional support for this proposition is found in the current Vaccine Injury Table, which still maintains a presumption of causation for encephalopathy/ encephalitis within 72 hours after receipt of "vaccines containing whole cell pertussis bacteria, extracted or partial cell pertussis, or specific pertussis antigen(s) (e.g., DTP, DTaP, P, DTP-Hib)." It does not distinguish between the forms of pertussis vaccine or state that the acellular toxoid is safer than the whole-cell toxin form.

[26] Dr. Wiznitzer stated only that "this article is not relevant since M.S.M. did not have a post-vaccination encephalopathy." He opined that M.S.M. in fact had pre-existing developmental delay, then received the vaccinations, and only had a "convulsion." Resp. Ex. B at 10-11. This opinion from Dr. Wiznitzer is more relevant to, and will therefore be discussed, under *Althen* prong two – whether there was a logical sequence of cause and effect reflecting that M.S.M.'s vaccines *did cause* her injury.

except for the two episodes of status epilepticus. Resp. Ex. B at 9-10, 12. As discussed below, under the section heading "alternative cause," I reject this argument because M.S.M. tested negative for any known pathogenic mutation in SCN1A or any other genes. Respondent cannot rebut vaccine causation by pointing to an "idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition." § 13(a)(2). Respondent's other expert Dr. Lobo was asked whether "every time a child has a seizure, it reduces their seizure threshold." He answered: "I don't know." Tr. 295.

B. Challenge-Rechallenge

Petitioner and Dr. Shafrir also argued that they did not need to establish a specific medical theory (i.e., mechanism of causation) because they have provided evidence of "positive rechallenge" in M.S.M.'s case. *See* Pet. Post-Hearing Brief at 17-18, citing *Capizzano v. Sec'y of Health & Human Servs.*, No. 00-759V, 2004 WL 1399178 (Fed. Cl. Spec. Mstr. June 8, 2004), *mot. for rev. den'd*, 63 Fed. Cl. 227, *vacated & remanded*, 40 F.3d 1317 (Fed. Cir. 2006), *on remand*, 2006 WL 3419789 (Fed. Cl. Spec. Mstr. Nov. 8, 2006).

In *Capizzano*, the special master explained that challenge-rechallenge occurs when a vaccine is followed by a medical injury, and when that vaccine is given again, the medical injury repeats or worsens. 2004 WL 1399178 at *2, n. 5. The special master cited a statement from the Institute of Medicine ("IOM")[27] that rechallenge is strong proof of causation. *Id.* at *2. He found particularly probative a medical article[28] reporting on four individuals who received Hepatitis B vaccine, developed rheumatoid arthritis ("RA"), received Hepatitis B vaccine, and then had worsened symptoms of RA. *Id.* The special master concluded that this journal article demonstrated that the hepatitis B can cause RA based on this evidence of rechallenge. *Id.* The Federal Circuit affirmed this determination: "the first prong of the [*Althen*] test was satisfied by the finding that hepatitis B vaccine can cause RA." 440 F.3d at 1326. The Federal Circuit then remanded the case to the special master, who wrote: "As found by the undersigned and affirmed by the Federal Circuit, the hepatitis B can cause RA based upon evidence in the medical literature of 'rechallenge' in other vaccine recipients." The special master then concluded that petitioner had established a logical sequence of cause and effect, including challenge-rechallenge, in her own case and was therefore entitled to compensation. *Capizzano*, 2006 WL 3419789, *15.

[27] The IOM's new name is the Health and Medicine Division ("HMD") within the National Academies of Sciences, Engineering, and Medicine ("the National Academies"). *See* National Academies – Health and Medicine Division – Our Web Address and Division Name, http://nationalacademies.org/hmd/About-HMD/Division-Name.aspx (last accessed July 30, 2019).

[28] J.F. Maillefert et al., *Rheumatic Disorders Developed After Hepatitis B Vaccination*, 38 Rheumatology 978-83 (1999). I have located this article through an internet search and it does indeed demonstrate challenge-rechallenge. It reads: "Six women developed an inflammatory polyarthritis satisfying the 1987 ARA criteria for the diagnosis of RA. They had received vaccination 1, 2, 3, 10, 18 and 20 days, respectively, prior to symptom onset. All received another injection. The symptoms worsened in four cases."

In the present case, Dr. Shafrir submitted two references which provide that evidence of positive rechallenge establishes causation with "certainty." Pet. Ex. 18 at 16.[29] These are consistent with the IOM's continued position on the significance of rechallenge to vaccination. In a more recent publication, the IOM provides: "[R]echallenge [is] an adverse event that occurred after more than one administration of a particular vaccine in the same individual. Each challenge in a patient, however, must meet the same attributes of reasonable latency, documentation of vaccination receipt, and clinician diagnosis of the health outcome."[30] In this case (as discussed further below under *Althen* Prong Two), M.S.M. developed febrile status epilepticus within a similar period of time after receiving DTaP, Hib, and PCV vaccinations on two separate occasions. Dr. Shafrir noted other times where M.S.M. had fevers but not seizures. It was only after receipt of those vaccinations that M.S.M. had both fever and status epilepticus. Dr. Shafrir did not file strong evidence of challenge-rechallenge in other individuals.[31] Thus, the evidence in this case may not be precisely the same as the proof of challenge-rechallenge establishing *Althen* prong one in *Capizzano*. However, the evidence of M.S.M. experiencing challenge-rechallenge meeting the IOM criteria, after receiving the same vaccines on two occasions, provides additional support for her experts' theory of how those vaccines cause fever, status epilepticus, and encephalopathy.

C. Theories Relating to Dravet Syndrome and SCN1A Gene Mutations

One complication of this case is that M.S.M.'s clinical picture resembles Dravet syndrome (otherwise known as severe myoclonic epilepsy of infancy, or "SMEI").[32] Dravet syndrome is a rare and distinct epileptic encephalopathy. Onset is during infancy, usually at about six months of age. Onset involves prolonged convulsions which are either generalized or hemiclonic, often associated with fever, and often classified as status epilepticus. The presentation later evolves to include other seizure types including focal, myoclonic, partial,

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[29] World Health Organization, *Pharmacovigilance Guidelines*, available at http://www.who.int/medicines/areas/quality_safety/safety_efficacy/S.AfricaDraftGuidelines.pdf [Pet. Ex. 20]; Edwards, I. Ralph & Jeffrey K. Aronson, *Adverse Drug Reactions: Definitions, Diagnosis, and Management*, 356 Lancet 1255 (2000) [Pet. Ex. 21].

[30] Institute of Medicine, *Adverse Effects of Vaccines: Evidence and Causality* (2012) at 13.

[31] Dr. Shafrir did file one article by Nouno et al. reporting that a portion of children (some with *no* history of convulsive disorders, and some with a history of convulsive disorders but no seizure activity for at least one year) showed an increase of epileptic spikes on EEG following administration with DPT vaccine and even with DT vaccine (without any pertussis component). DT vaccine was also associated with redness and swelling at the injection site as well as fever. Nouno S. et al., *Adverse Effects on EEG and Clinical Condition after Immunizing Children with Convulsive Disorders*, 32 Acta Paediatr. Jpn. 357-60 (1990) [Pet. Ex. 30]. Nouno et al. recommended delaying vaccination until after 3 years of age for children with convulsive disorders. While these children showed an increase of epileptic spikes, that was not associated with any symptoms such as seizures. Additionally, this does not meet the definition of challenge-rechallenge (which requires two administrations of the vaccine(s), each followed by a worsening of symptoms).

[32] *See* Pet. Ex. 2 at 50-51 (November 2013 EEG report first raising this diagnosis); Pet. Ex. 2 at 54-55 (December 2013 record by neurologist Dr. Reese, recommending testing of the SCN1A gene because a positive finding would inform the treatment plan); Tr. 14 (testimony of petitioner's expert neurologist Dr. Shafrir); Tr. 177 (testimony of respondent's expert neurologist Dr. Wiznitzer).

absence, and atonic. Children with Dravet syndrome typically display normal development before the onset of seizures, as well as initially after. But beginning in the second year of life, they display developmental delay or regression.[33] Approximately 70 - 80% of children with Dravet syndrome who undergo genetic testing are found to have a mutation in the SCN1A gene.[34] The SCN1A gene encodes the α1 subunit of the neuronal sodium channel and is described as "the most relevant epilepsy gene with the largest number of epilepsy-related mutations."[35]

Within the Vaccine Program, there have been numerous cases in which petitioners allege that DTaP along with other vaccines routinely administered during the first year of life either *cause* or *significantly aggravate* the course of Dravet syndrome. In those cases, the vaccinated children undergo genetic testing and are found to have mutations in the SCN1A gene. In those cases, the special masters (as well as judges at the Court of Federal Claims and the Court of Appeals for the Federal Circuit) have consistently concluded that the alleged vaccine injuries are attributable to the SCN1A mutations and are not caused or aggravated by any vaccines.[36]

In this case, treating physicians recorded that M.S.M.'s clinical picture was consistent with Dravet syndrome. However, Dr. Shafrir opined that M.S.M.'s clinical picture was "similar" but had "some clinical differences" from Dravet syndrome. Pet. Ex. 85 at 37-38; Tr. 14. And as discussed further below, M.S.M. had significant developmental delay within days of her initial status epilepticus. This is unlike Dravet syndrome, in which onset is during infancy but developmental delay typically manifests later, beginning in the second year of life (according to the previously cited literature). Most importantly, her treating pediatric neurologist Dr. Reese and Dr. Shafrir upon being consulted for a second opinion on her treatment recommended genetic testing to "confirm" the suspicion of Dravet syndrome and to inform which medications she should or should not take. Eventually, M.S.M. underwent sequencing of the SCN1A gene which was negative for any known mutations. She then underwent a second more comprehensive epilepsy panel. Apart from one missense variant of unknown significance, the test was entirely negative for known epileptogenic mutations. Pet. Exs. 17, 63.

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[33] *See, e.g.*., Passamonti C. et al., *A Novel Inherited SCN1A Mutation Associated with Different Neuropsychological Phenotypes: Is There A Common Core Deficit?*, 43 Epilepsy in Behavior 89 (2015) [Pet. Ex. 65]; McIntosh A. et al., *Effects of Vaccination on Onset and Outcome of Dravet Syndrome: A Retrospective Study*, 9 Lancet Neurology 592 (2010) [Pet. Ex. 23].

[34] Passamonti [Pet. Ex. 65]; *see also* Hoffman-Zacharska D. et al., *From Focal Epilepsy to Dravet Syndrome – Heterogeneity of the Phenotype Due to SCN1A Mutations of the p.Arg1596 Amino Acid Residue in the Nav1.1 Subunit*, 49 Polish Jounral of Neurology and Neurosurgery 258 (2015) [Pet. Ex. 66].

[35] Passamonti [Pet. Ex. 65] at 1.

[36] *See, e.g., Oliver v. Sec'y of Health & Human Servs.*, No. 10-394V, 2017 WL 747846 (Fed. Cl. Spec. Mstr. Feb. 1, 2017), *mot. for rev. den'd*, 133 Fed. Cl. 341 (2017), *aff'd*, 900 F.3d 1357 (Fed. Cir. 2018); *rehearing en banc den'd*, 911 F.3d 1381 (Fed. Cir. 2019). In Chief Special Master Dorsey's underlying decision in *Oliver*, footnote 3 provides a list of approximately 15 cases which had been denied as of the date of her decision. Consistent with this line of cases, I (Special Master Gowen) is also unlikely to be persuaded of vaccine causation where there is a confirmed SCN1A gene mutation. *See, e.g. Bales v. Sec'y of Health & Human Servs.*, No. 15-882V, 2017 WL 6334786 (Fed. Cl. Spec. Mstr. Nov. 15, 2017) (dismissing the claim for insufficient proof in light of a SCN1A gene mutation).

Given the negative findings on relevant epileptogenic genes and the clinical variance in the presentation, there is insufficient evidence to attribute M.S.M.'s condition to a genetically-driven Dravet Syndrome or other seizure disorder. Accordingly, the theories and responses involving that condition do not fit this case and will not be discussed further.

D. Evaluation of the Evidence

Throughout this case, Dr. Shafrir and Dr. Bellanti opined that vaccines activate an innate immune response involving the production of pro-inflammatory cytokines, in particular Il-1, which can cause fever. In a susceptible individual, the same innate response, pro-inflammatory cytokines, and fever can cause status epilepticus. Respondent's experts conceded that in this case, M.S.M. did in fact receive vaccines on March 11, 2013, which caused her to develop fever and status epilepticus. They further conceded that M.S.M. received several of the same vaccines on December 26, 2013, which again caused fever and status epilepticus.

Dr. Shafrir, a well-qualified neurologist and epileptologist, opined that status epilepticus can lower the threshold for further seizures. In this case, M.S.M.'s initial febrile, tonic-clonic seizure was sufficiently severe and lasted long enough to be classified as status epilepticus by her treating physicians. This first seizure more likely than not reduced the seizure threshold and can be said to give rise to all of the rest. Respondent did not challenge this principle and it appears to be well supported by the testimony and literature.[37] Accordingly, I conclude that petitioner has satisfied *Althen* prong one.

2. *Althen* Prong Two: Logical Sequence of Cause and Effect

To fulfill *Althen* prong two, petitioner must show, by a preponderance of the evidence, "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e., in this particular case, did the vaccine(s) cause the alleged injury. *Broekelschen*, 618 F.3d at 1345 ("Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case"). Temporal association alone is not evidence of causation. *See Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). This sequence of cause and effect is usually supported by facts derived from petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992).

[37] *See also Swaiman's Pediatric Neurology: Principles and Practice* (4th ed. 2006) at 271 ("Adverse Effects of Seizures on the Developing Brain… Overall, emerging evidence suggests that seizures early in life can result in permanent behavior changes and enhanced epileptogenicity, although the mechanisms of some seizure-induced dysfunctions have not been clearly delineated.").

A. Evaluation of the Evidence

i. M.S.M.'s Development before First Status Epilepticus

a. Primary Care Records

The parties' respective experts in neurology agreed that M.S.M. presently has an epileptic encephalopathy. *See* Tr. 123. Petitioner's expert in neurology Dr. Shafrir opined that injury began with her March 11, 2013 vaccinations. Respondent's expert in neurology Dr. Wiznitzer countered that M.S.M.'s injury predated those vaccinations. This dispute centered on two sources of medical records.

First are the pre-vaccination records from the *only* medical provider who treated M.S.M. before her first status epilepticus, her primary care provider Dr. Cruz. On the date of vaccinations, he recorded "generalized hypotonia but normal milestones" including sitting alone and reaching for toys. Petitioner's expert Dr. Shafrir opined that hypotonia is one indicator of gross motor development. It is based on the provider's subjective assessment of whether the child's body feels "loose" upon passive manipulation. However, it is unusual for a child with hypotonia to sit alone, which M.S.M. was able to do. Pet. Ex. 18 at 3; Tr. 16, 29-31.

Dr. Shafrir also opined that hypotonia is a very common finding. It is likely insignificant if development is otherwise normal. In M.S.M.'s case, prior to administering the vaccines, the primary care provider recorded that her development was normal and circled that she was meeting many of the developmental milestones for her age of six months. Additionally, the primary care provider did not record a referral to neurologist. Tr. 48-49. And upon being contacted by a resident at the hospital about M.S.M.'s first status epilepticus on March 12, 2013, the primary care provider advised that she did not have any preexisting developmental delay. Tr. 31. Therefore, Dr. Shafrir did not see "any reliable evidence from the records that M.S.M.] had developmental delay before her immunizations." Pet. Ex. 64 at 1.

Respondent's expert neurologist Dr. Wiznitzer opined that hypotonia signifies "something going on with the nervous system." Hypotonia in the presence of "good strength and elicitable reflexes" is not coming from the spinal cord, muscles, or nerves, but is instead "coming from the brain." Tr. 124-28. Central nervous system hypotonia would be consistent with a "static encephalopathy." Tr. 207.

Dr. Wiznitzer agreed that hypotonia is a measure of "excessive movement of joints and extremities" on passive manipulation. Dr. Wiznitzer opined that there are certain methods for objective, precise assessment of hypotonia that are published in medical literature and are taught to some medical providers. However, Dr. Wiznitzer "ha[d] no idea how" the primary care provider concluded that M.S.M. had hypotonia. Tr. 124-28, 207-14. And on cross-examination, Dr. Wiznitzer acknowledged that in M.S.M.'s records, "some people described hypotonia... Others don't. It's variable. And that is... one of the problems we have and why we're trying to do an educational program... so people do things the right way." Dr. Wiznitzer also acknowledged that Dr. Reese – a pediatric neurologist – did *not* record that M.S.M. had hypotonia on at least one occasion. Tr. 209-10.

The primary care provider did indeed record "generalized hypotonia" on March 11, 2013. Indeed, that observation is repeated in his later post-vaccination and status epilepticus records. However, that appears to be a subjective measure. The provider did not record how he reached that conclusion or find it to be sufficiently concerning to refer M.S.M. to a neurologist. Indeed, he recorded otherwise normal milestones both in his written records and by circling several six-month old developmental milestones on the Denver chart. The parties' expert neurologists are both well-qualified in assessing developmental delay. However, I find Dr. Shafrir's explanation to be more persuasive. I conclude that the notation of "generalized hypotonia" does not demonstrate that M.S.M. had developmental delay or encephalopathy before the March 11, 2013 vaccinations.

b. Hospital Records

Respondent's expert Dr. Wiznitzer opined that the hospital records also showed that M.S.M. had developmental delay *before* the March 11, 2013 vaccinations, status epilepticus, and that hospital admission. Resp. Ex. B at 12. He focuses on the following record made by a pediatrician at the hospital on March 12, 2013 at 5.30 p.m.:

> Pt. was awake and alert in her crib. She engaged with the examiners, smiled, and vocalized. Neuro exam was significant for gross motor delays (doesn't reach for toys, unable to sit without support, head bobbing noted when in sitting position) – *all present at baseline per parents…*
>
> Assessment: 6 mo s/p complex febrile seizure with no source of fever on exam, *now well-appearing and back to baseline per parents*. Fever was likely secondary to immunizations. Exam and hx are notable for motor delay (fine and gross.)

Pet. Ex. 10 at 21-22 (emphasis added); referenced at Resp. Ex. B at 4, 12 (Dr. Wiznitzer's report); Tr. 129-30, 211-14 (his testimony). Dr. Wiznitzer asserted: "The developmental delay was identified… by history from her parents, not by direct examination [at the hospital]. The Denver Developmental Screening Test also uses parental report for many of its milestones in infancy. Therefore, the information was by parental report and would not be affected by any sedation after her seizures." Resp. Ex. B at 12.[38] Dr. Wiznitzer also stated that the parents' Spanish language and need for an interpreter would not have compromised the accuracy of the medical records. He stated that Spanish-speaking patients routinely communicate with medical providers who can speak Spanish themselves or with assistance from interpreters. The communication in Spanish would not necessarily be noted in each particular medical record. Tr. 132-33.

Petitioner's expert Dr. Shafrir disagreed that the hospital records offered any evidence of preexisting developmental delay. He questioned whether it was useful to assess a child's development "immediately following prolonged status epilepticus with several doses of

[38] *See, e.g., Denver II Training Manual*, at www.DenverII.com [Resp. Ex. R] at 9.

benzodiazepines" in an unfamiliar environment. All of these factors would decrease the child's awareness, comfort, and ability to respond to assessment prompts.[39]

Dr. Shafrir thought the parents' Spanish language was relevant and might have caused confusion. I tend to agree with Dr. Shafrir that terms such as "baseline" could be confusing to parents whose primary language is English and even more confusing to parents whose primary language is not English and who are depending medical providers and/or interpreters to accurately pose the questions and understand the answers.

More importantly, Dr. Wiznitzer's representation of the hospital records is not accurate. First, he says the child's history is obtained "by history from her parents," but the record above reflects that the doctors also conducted a neurological exam. Pet. Ex. 10 at 21-22. There is some ambiguity in their notation, repeated here: "Neuro exam was significant for gross motor delays (doesn't reach for toys, unable to sit without support, head bobbing noted when in sitting position) – *all present at baseline per parents*." Pet. Ex. 10 at 21. Dr. Wiznitzer's interpretation is that the parents reported that at M.S.M.'s previous baseline, she had these delays - she could *not* reach for toys, could *not* sit without support, *and* her head bobbed.

A more likely interpretation is that the doctors observed that M.S.M. could not reach for toys, she could not sit without support, and her head bobbed, but the parents reported that she *was* previously able to do those things at baseline. This interpretation is consistent with the Denver Development manual, which provides that a medical provider is supposed to personally observe a child's ability to "work for toy"; "sit, no support"; and "sit, head steady." A medical provider is not supposed to accept parental report for these measures. Resp. Ex. B at 17, 30, 31.

Other hospital records reflect that the parents did not report prior developmental delay. For example, a different physician recorded: "per report, [M.S.M.] was born on time and has been meeting developmental milestones at her pediatrician's." Pet. Ex. 10 at 16. Another record provides: "no h/o neurodevelopmental delay." *Id.* at 20. Another record provides: "small head lag when pulled to sit, when held sitting head is off-center/lopsided as if unable to hold central firm (different from baseline per dad)." *Id.* at 21.

Additionally, as noted above, her primary care provider Dr. Cruz recorded one day before the hospitalization, on March 11, 2013, that M.S.M. was able to work for a toy and sit alone. He circled the achievement of these milestones on a Denver chart. *See* Pet. Ex. 1 at 10, 21. A medical student at the hospital recorded calling Dr. Cruz, who reported that M.S.M. did not have "any developmental delay at her 4 month or 6 month visits." Pet. Ex. 10 at 30.

In short, the hospital records do not support a finding of developmental delay preexisting the first status epilepticus. They more likely represent developmental delay beginning after the status epilepticus.

[39] *See, e.g., Denver II Training Manual* [Resp. Ex. R] at 9 (providing that "the examiner's efforts should be directed toward obtaining the best test performance possible… every effort should be made to make the caregiver and child comfortable").

ii. M.S.M.'s Development after the First Status Epilepticus

Petitioner's expert neurologist Dr. Shafrir opined that on March 12, 2013, M.S.M. experienced seizure activity for over thirty (30) minutes. This constituted status epilepticus, as recorded in the hospital records and agreed upon by Dr. Wiznitzer. Pet. Ex. 10 at 46-49; Pet. Ex. 64 at 1-2; Tr. 135. M.S.M. was admitted on March 12 and discharged on March 14, 2013, resulting in a hospitalization for over twenty-four (24) hours. Pet. Ex. 10 at 4-7.[40]

Dr. Shafrir opined that the hospital records establish "that M.S.M. suffered encephalopathy with the loss of previously achieved developmental milestones that were recorded on the day prior to that admission." Pet. Ex. 64 at 1-2.

As discussed above, I have found that M.S.M. did not have any developmental delay beforehand. On March 11, 2013, her primary care provider Dr. Cruz recorded that she had generalized hypotonia which Dr. Shafrir did not find significant in light of the achievement of normal development for her age of six months per a Denver developmental evaluation. She could work for toy out of reach, transfer toy to hand, feed self crackers, roll over belly to back, sit without support, and had no head lag when pulled to sitting. Pet. Ex. 1 at 5, 21. Importantly, these observations were made by a doctor who was familiar with M.S.M. and in a non-traumatic setting, unlike the post-vaccination evaluation in the hospital.

On March 12, 2013, M.S.M. experienced febrile status epilepticus and was hospitalized. While in the hospital, several physicians separately observed that she was *not* reaching or grasping for toys. She did not roll over. She did not sit alone. She also had a small head "lag" or "bob" when pulled to a sitting position. *See, e.g.*, Pet. Ex. 10 at 19, 21-22. She was found to have gross and fine motor developmental delay. *Id.* at 5, 19, 21-22.[41] The hospital discharge summary provided: "needs continued follow-up for mild developmental delay, consider refer[r]al to infants and toddlers." *Id.* at 7. On March 15, 2013, her primary care provider Dr. Cruz saw M.S.M. but did not evaluate her development. Pet. Ex. 1 at 6.

On April 22, 2013, a pediatric neurologist, Dr. Reese, conducted an initial evaluation with M.S.M. He recorded the mother's statement that M.S.M. was "back to her normal self since returning from the hospital." Pet. Ex. 2 at 31. Respondent's expert Dr. Wiznitzer contends that this reflects that there was "no change in her condition before the seizure and then after she came home after the seizure." Tr. 145. This seems to be an overread by Dr. Wiznitzer of a general statement from the mother, who more likely was reporting that her child was not having continued seizures (the condition for which they were seeing Dr. Reese for the first time). It seems unlikely that the mother's general statement reflects her comprehensive view of the child's health including developmental milestones. Dr. Reese had never seen M.S.M. before the status epilepticus. Additionally, Dr. Reese recorded – consistent with the post-status epilepticus hospital records – that M.S.M. could not sit alone. Pet. Ex. 2 at 31-33. This actually

[40] In his first report, Dr. Wiznitzer incorrectly stated that M.S.M. was discharged in less than 24 hours, on March *13*, 2013. Resp. Ex. B at 9.

[41] Respondent's expert Dr. Shafrir opined that these observations "would not be affected by any sedation after her seizures." Resp. Ex. B at 12.

corroborates that M.S.M. had new developmental delay following the vaccines and the first status epilepticus.

On April 24 and May 10, 2013, Dr. Cruz saw M.S.M. but did not evaluate her development. Pet. Ex. 1 at 7-8. On June 11, 2013, Dr. Cruz repeated the Denver developmental evaluation. She reached for a toy but had she decreased mobility of the left arm. She could no longer roll over or sit alone. Dr. Cruz concluded that M.S.M. had gross motor developmental delay and referred her to the Maryland Infants and Toddlers Program, which offers early intervention services for young children with developmental delays and disabilities.[42] Pet. Ex. 1 at 9. On July 17, 2013, their initial evaluation found that M.S.M. had at least 25% delay in gross and fine motor developmental delay. Pet. Ex. 12 at 1-2. She began physical therapy, occupational therapy, and speech therapy. *See generally* Pet. Ex. 12.

These records establish that following the vaccines and the first status epilepticus on March 12, 2013, M.S.M. had the new onset of decreased gross and fine motor development. The March 12 – 14, 2013 hospital records reflect these losses and suggested referral to Maryland Infants and Toddlers for therapy. They were corroborated in April 2013 by the neurologist and in June 2013 by the primary care provider who then referred M.S.M. for the needed necessary therapy. This sequence of events seems logically caused by the febrile status epilepticus on March 12, 2013, which was caused by the vaccines, as conceded by respondent's experts. Pet. Ex. EE at 3-4; Tr. 250-51, 53-54 (Dr. Lobo); Tr. 135, 142-44, 227 (Dr. Wiznitzer).

It is also noted that M.S.M. underwent radiology during this time. On May 2, 2013, an MRI of the brain showed "no brain abnormality" but there was "reduced resolution of the internal architecture of the brain… secondary to age-related isointensity of the gray and white matter." The radiologist advised that if M.S.M.'s condition persisted, she should undergo a follow-up MRI when she was at least two years old to obtain better imaging. Pet. Ex. 2 at 33. Dr. Shafrir and Dr. Wiznitzer agreed that some aspects of the brain are not visible on MRI, with a child that young. Pet. Ex. 64 at 3; Tr. 148-51.

M.S.M. also underwent a basic EEG on July 3, 2013, Pet. Ex. 2 at 39-40 (providing that the findings "suggest lower seizure threshold"), and a video EEG on November 21, 2013, Pet. Ex. 2 at 50-51. Dr. Shafrir opined that the findings were consistent with a diagnosis of encephalopathy and would have been present if an EEG was performed earlier, closer in time to the initial status epilepticus on March 12, 2013. Pet. Ex. 64 at 2; Tr. 18-19. Dr. Wiznitzer opined that the EEGs showed epileptiform activity coming from multiple areas of the brain, which was more consistent with "abnormalities at the synaptic level, where the cells talk to each other and how they deal with each other, rather than from some much larger inflammatory process." Tr. 151-54. Upon my review, all that can be said is that the EEGs showed a "lowered seizure threshold" and were consistent with an encephalopathy, although that cannot be definitively said to be the cause.

[42] *Maryland Infants and Toddlers Program*, https://referral.mditp.org/ (last accessed July 30, 2019).

iii. Rechallenge

Petitioner and Dr. Shafrir argued that M.S.M. experienced challenge-rechallenge. Indeed, similar to March 2013, in December 2013 M.S.M. received several of the same vaccinations (DTaP, Hib, and PCV but not IPV or rotavirus), and within less than 24 hours, she developed a similar fever (over 102 degrees Fahrenheit) and convulsive seizure.

The records reflect that M.S.M. had a brief 5-minute seizure which prompted her parents to call an ambulance. M.S.M. had the more pronounced seizure in question as she was brought into Holy Cross Hospital. The ambulance reached the hospital at 5:23 a.m. and transferred care at 5:32 a.m. Pet. Ex. 10 at 254-56. The seizure stopped at 6:00 a.m. Pet. Ex. 10 at 40. Thus, it likely lasted for at least 30 minutes.

Dr. Shafrir opined that this seizure at the hospital constituted status epilepticus. Pet. Ex. 18 at 15; Pet. Ex. 64 at 2, 7-8; Pet. Ex. 92 at 2. He opined that the classic definition of status epilepticus is a seizure lasting for more than thirty minutes, which did occur here. He added that the American Epilepsy Society is shortening the time period to under 30 minutes. Tr. 27, 57-58.[43] He also noted that her pediatric Glasgow Coma score of 10 (on a scale of 0 to 15, with the lowest scores being the worst), reflected a decreased level of consciousness. Tr. 57, citing Pet. Ex. 10 at 236. Dr. Shafrir opined that this second seizure episode following DTaP, Hib, and PCV "confirm[ed] a causal relationship." Pet. Ex. 18 at 16.[44] "It is clear from the medical records that [M.S.M.] has not suffered any other episodes of status epilepticus." *Id.* He opined that this showed the specificity of the response to the DTaP, Hib, and PCV vaccinations. Tr. 46.

Dr. Bellanti opined that because M.S.M. had a suspected reaction to the vaccines in March 2013, she should not have received them again in December 2013. Tr. 93. He agreed that the second, similar episode of prolonged febrile seizure within a similar period of time after several of the same vaccines was "striking," and supported a logical sequence of cause and effect in her case. Tr. 103.

Respondent's expert neurologist Dr. Wiznitzer said that it was not contraindicated to repeat administration of the vaccines that were associated with status epilepticus in March 2013. Tr. 160-61. Dr. Wiznitzer agreed that "the second seizure [on December 27, 2013, in the emergency room] may have been long enough that it, by itself, fulfilled a criteria for status epilepticus." Tr. 164-65.

iv. Significance of Levetiracetam

Dr. Wiznitzer argued that M.S.M.'s second status epilepticus did not constitute "rechallenge" because there was a confounding factor: she had missed doses of her

[43] Dr. Shafrir opined that another benchmark of status epilepticus is if the medical providers find that it is necessary to administer benzodiazepine. Tr. 27-28. That was not administered to stop M.S.M.'s seizure, although she was discharged with a one-day supply of diastat. Pet. Ex. 10 at 246.

[44] Citing World Health Organization [Pet. Ex. 20]; Edwards [Pet. Ex. 21].

anticonvulsant seizure medication levetiracetam (Keppra). Resp. Ex. B at 9-10. He opined that "had [M.S.M.] been taking her medicine, she would not have had that seizure." Tr. 166. He also opined that an IV infusion of levetiracetam stopped her seizure activity in the hospital. Tr. 166. He also opined that after December 27, 2013, M.S.M. followed the prescription for levetiracetam and her condition significantly improved. Tr. 166.

Dr. Shafrir disagreed. He opined that challenge-rechallenge is a clinical fact. One can always look for alternative explanations for an adverse event, but he did not believe that M.S.M.'s missing levetiracetam was an explanation for this event. After the onset of her seizure activity (the vaccine-related status epilepticus on March 11, 2013), M.S.M. only had myoclonic and atonic seizures. This included a 2-3 minute episode in April 2013, and then episodes of head drop, eye fluttering, and leg jerks beginning in October 2013. That prompted Dr. Reese's prescription of levetiracetam for the first time on December 3, 2013. Because of the absence of prolonged seizures between March – early December 2013, before levetiracetam was introduced, it cannot be said that levetiracetam was responsible for preventing such seizures or that less than therapeutic levels of the drug caused the second seizure. Pet. Ex. 65 at 5-7; Tr. 24, 63-64.

Dr. Shafrir also opined: "If [M.S.M.] was on a very high level of [levetiracetam,] maybe the status epilepticus would have been prevented. But… the seizure is not caused by a low level of anti-epileptic medication unless it [is] stopped abruptly." Tr. 63. Generally, "seizures are caused by whatever causes seizure," whether or not M.S.M. was taking levetiracetam, this "would still be a status epilepticus following the same set of immunizations." Tr. 63-64.

Upon review, I am inclined to agree with Dr. Shafrir. He is correct that M.S.M. did not have any episodes of prolonged, generalized seizure for nine months before she was prescribed levetiracetam by her neurologist. He did not record his reasoning for prescribing levetiracetam, but it seemed to be for controlling the short episodes of head drop, eye fluttering, and leg jerk. Additionally, there is no indication that M.S.M. took levetiracetam consistently for any length of time. It was prescribed for the first time on December 3, 2013. Ten days afterwards, her primary care provider Dr. Cruz recorded that when M.S.M. took levetiracetam, she didn't have "seizures," but sometimes she refused to take it and she had "seizure activity." Pet. Ex. 1 at 13. Seventeen days later, the neurologist Dr. Rese recorded that the mother had expressed hesitancy about taking it. Pet. Ex. 2 at 53. Twenty-four days later, she had the status epilepticus and levetiracetam was found to be below therapeutic levels. Dr. Wiznitzer acknowledged that "abruptly" stopping anti-seizure medication can potentially cause seizure, but it is more likely that M.S.M. was never consistently taking levetiracetam in the first place. In conclusion, I find that the lack of levetiracetam was not a substantial factor in causing the second status epilepticus. That was more logically caused by the repeat administration of the vaccines.

v. Significance of Fever

Dr. Wiznitzer and Dr. Lobo opined that fever was a "plausible mechanism" for M.S.M.'s prolonged seizures. *See, e.g.*, Resp. Ex. B at 10. They in fact conceded that the March 11, 2013 vaccines caused M.S.M. to develop a fever which was measured at 102.8 degrees Fahrenheit as well as status epilepticus. The December 26, 2013 vaccines caused M.S.M. to develop a fever that was measured at 102.2 degrees Fahrenheit as well as status epilepticus.

Dr. Shafrir opined that "fever is definitely a precipitant for seizure" in susceptible individuals such as M.S.M. Tr. 35. He noted that in the absence of vaccines, M.S.M. did have fevers that were lower and not associated with prolonged seizure episodes. Specifically, in April 2013, M.S.M. was asleep, then suddenly screamed, went limp, and all of her limbs shook. She stopped breathing, drooled, and vomited. The episode lasted between two to three minutes. She was transported to the emergency room, where she was "alert and smiling" with "no postictal phase." Her temperature was 101.1 degrees Fahrenheit. Pet. Ex. 10 at 164-91.

Second, in May 2014, M.S.M. went to the hospital where her temperature was measured at 100.0 degrees Fahrenheit, in association with hives and a viral syndrome. This low-grade fever was not associated with any seizure activity. Pet. Ex. 10 at 199-232.

Therefore, Dr. Shafrir opined that "not every fever caused seizures" in M.S.M. This contributed to his view that there was something unique about the vaccines and the response that they activated. Pet. Ex. 18 at 16; Tr. 35. I am inclined to agree. It is striking that the two vaccinal fevers were considerably higher than the fevers documented at other times and were associated with more significant seizure activity.

vi. Subsequent Clinical Course

Dr. Shafrir opined that M.S.M.'s second status epilepticus "probably caused further damage to the brain and further acceleration of her epileptic encephalopathy." Tr. 46. Dr. Wiznitzer disagreed, opining that that M.S.M. "went right back to baseline right after that seizure… She wasn't even admitted. There was no alteration or change in her developmental course [or…] in her epilepsy… her epilepsy was better, not worse." Tr. 225-26. This was not particularly developed in the reports and the testimony, but it is clear that M.S.M. continued to have developmental delays, for which she continued physical and speech therapy through the Maryland Infants and Toddlers program. Her neurologist increased levetiracetam several times but her seizure activity was not fully controlled. The parents obtained a second opinion from Dr. Shafrir in part because they were disappointed by her lack of progress. Thus, it is likely that that second status epilepticus did not help her clinical course.

vii. Treating Physicians' Opinions

Dr. Wiznitzer correctly noted that the treating neurologist did not believe that M.S.M.'s vaccines caused or aggravated her condition. Resp. Ex. B at 10. The treating physician's opinion is noted, but not determinative for several reasons. First, the treating neurologist never saw M.S.M. before the first vaccinations at issue and the first status epilepticus; therefore, he did not have the opportunity to assess her condition before compared to after. In my view, there is a marked change with loss of several developmental milestones after the vaccines and status epilepticus. Additionally, the neurologist does not fully consider the two episodes of vaccines-fever-status epilepticus. He recorded that the second episode happened one day after vaccines – but does not detail how long she was actively seizing in the hospital or the similarities to the first acute episode. Pet. Ex. 2 at 69 (only describing the short episode at the home, which prompted the family to go to the hospital). Finally, the neurologist was focused on a genetic explanation

such as an SCN1A mutation which would confirm the suspicion of Dravet syndrome, but no genetic explanation has been found.

viii. Conclusion

In summary, in March 2013, M.S.M. was a healthy six-month-old child with no history of seizure activity. She was recorded to have "generalized hypotonia." However, that was a subjective measure which did not correspond to her achievement of many specific, observed developmental milestones for her age. Her primary care provider did not record concern or a referral to a neurologist based on these findings. I conclude that she did not have developmental delay. After M.S.M.'s vaccines caused fever and status epilepticus, she had developmental delay necessitating referral to physical and speech therapy. This was recorded in the hospital and later by her primary care provider and her new neurologist. In December 2013, she received many of the same vaccines and experienced another episode of febrile status epilepticus within a similar period of time, which constituted positive rechallenge. This second episode was not explained by her lack of levetiracetam. There were a few other documented fevers which were not associated with the same type of prolonged febrile seizures seen with the vaccines. The treating neurologist believed her condition had a genetic explanation, but none was found. Based on all of the above, I find that petitioner has established a logical sequence of cause and effect between the vaccines in question and the injury alleged.

3. *Althen* Prong Three: Medically Acceptable Temporal Relationship

Althen prong three requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 543 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

A. Evaluation of the Evidence

Petitioner argued that there was an acceptable temporal relationship between M.S.M.'s third DTaP, Hib, IPV, PCV, Hep B, and rotavirus vaccinations received on March 11, 2013 and the onset of fever and status epilepticus within approximately 16 hours.[45] There was a similar

[45] The medical record does not indicate the time at which the vaccines were given. Pet. Ex. 1 at 5. Four days later, the provider submitted a VAERS report which provides that the vaccines were given on March 11, 2013 at 11:30 a.m. Pet. Ex. 1 at 31. Certain medical records indicate that the parents reported at approximately 10:00 p.m., M.S.M. had a one-minute staring episode after which she fell asleep. Pet. Ex. 10 at 19. The treating physicians and experts in the case did not assign much significance to this event. The records more clearly establish that on March

temporal relationship between M.S.M.'s fourth DTaP, Hib, and PCV vaccinations received on December 26, 2013 and the fever and status epilepticus the following day.[46]

Dr. Shafrir submitted an article by Skowronski et al.[47] for the proposition that DTaP is associated with an immune reaction, specifically swelling at the injection site, within 2 – 3 hours afterward. Pet. Ex. 64 at 4; Tr. 33-34. He also noted that the Vaccine Injury Table lists diphtheria-tetanus-pertussis in association with encephalopathy within 0 – 72 hours. Tr. 33-34.

As referenced above, Dr. Shafrir opined that the innate immune system plays an important role in the development and further flares of seizure disorders such as epilepsy. Pet. Ex. 64 at 4-5.[48] Vaccines activate the innate immune system including the production of pro-inflammatory cytokines which can cause fever and in some vulnerable individuals, seizure activity. Thus, the innate immune system can cause the injury on its own. Pet. Ex. 64 at 4-5.[49]

Dr. Bellanti opined that "if innate immune injury contributed to the pathogenesis of the inflammatory response, it would occur in less than 24 hours and would be consistent both with the child's early onset of symptoms and the development of fever following the administration of the DaPT vaccine." Pet. Ex. 95 at 6.

Respondent's experts devoted significant attention to critiquing Dr. Shafir's first theory, which was that the vaccines would cause an adaptive immune response involving the production of antibodies which would cross-react with brain proteins (due to molecular mimicry between the vaccines and the brain proteins) to cause seizure. Respondent's experts objected that this could not occur within the period of time seen in M.S.M.'s case. *See* Resp. Ex. B at 10; Resp. Ex. S at 3.

12, 2013 at approximately 3:00 a.m., M.S.M. had an episode of status epilepticus lasting for at least 20 minutes. Upon admission to the hospital, she had a rectal temperature of 102.8 degrees Fahrenheit. Pet. Ex. 10 at 46-51.

[46] Again, the medical record does not indicate the time at which the vaccines were given. Pet. Ex. 1 at 14. Without any further evidence, I would assume that it was sometime during normal business hours, e.g., on December 26, 2013 sometime between 9:00 a.m. and 5:00 p m. She was delivered to the hospital, actively seizing, at December 27, 2013 at 5:50 a m. Pet. Ex. 10 at 235-40.

[47] Skowronski D. et al., *Injection-Site Reactions to Booster Doses of Acellular Pertussis Vaccine: Rate, Severity, and Anticipated Impact*, 112 Pediatrics e453 (2003) [Pet. Ex. 69];

[48] Matin N. et al., *Epilepsy and Innate Immune System: A Possible Immunogenic Predisposition and Related Therapeutic Implications*, 11 Human Vaccines & Immunotherapeutics 2021-29 (2015) [Pet. Ex. 70]; Iori V. et al., *Modulation of Neuronal Excitability by Immune Mediators in Epilepsy*, 26 Curr. Opin. Pharmacol. 118-23 (2016) [Pet. Ex. 71].

[49] Kashiwagi Y. et al., *Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT), Haemophilus Influenzae Type B (Hib), and 7-Valent Pneumococcal (PC7) Vaccines*, 10 Hum. Vaccin. Immunother. 677-85 (2014) [Pet. Ex. 74]; Blood-Siegfried J. et al., *Monokine Production Following In Vitro Stimulation of the THP-1 Human Monocytic Cell Line with Pertussis Vaccine Components*, 18 J. Clin. Immunol. 81-88 (1998) [Pet. Ex. 75].

Respondent's experts agreed that the innate immune response could occur and cause status epilepticus within this short period of time. Dr. Wiznitzer testified that the innate immune response, including activation of pro-inflammatory cytokines and the development of fever, occurs within "the first minutes to hours, maybe even a day or so, of response to infection." Tr. 253-56. Dr. Wiznitzer agreed that the fever caused status epilepticus. Tr. 135, 142-44, 227.

Similarly, Dr. Lobo opined: "Innate immunity is indeed rapid, providing some immune protection before the adaptive response can take over some days or weeks later. The only plausible theoretical link between an innate response to the vaccine and [M.S.M.'s] first seizure is the induction of fever, which is an expected consequence of all effective vaccines." Resp. Ex. EE at 3. At the hearing, Dr. Lobo "explained that the innate immune response activates within minutes to hours after exposure to an infection, and that this response causes the production of IL-1 and a fever". Resp. Post-Hearing Brief at 9, citing Tr. 253-54.

Upon consideration of the evidence submitted and particularly in light of respondent's experts agreement that the innate immune response can occur within the timeframe seen in M.S.M., I conclude that petitioner has established *Althen* prong three.

4. Alternative Cause

Once petitioner establishes each of the *Althen* factors by preponderant evidence, the burden of persuasion shifts to respondent, who must show that the alleged injury was caused by a factor unrelated to the vaccination. *Knudsen*, 35 F.3d at 548; § 13(a)(1)(B). Respondent must demonstrate "[t]he factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." *Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated do "not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition."

A. Evaluation of the Evidence

Respondent contended that M.S.M. had an acute onset epileptic encephalopathy caused by a genetic mutation. Early on, the treating physicians recommended testing for mutations in the SCN1A gene, which is found in a majority of patients with a particular seizure disorder, Dravet syndrome. *See, e.g.* Pet. Ex. 2 at 54-55 (December 2013 record by treating neurologist); Pet. Ex. 2 at 61 (January 2014 record by treating geneticist). In April 2015, testing for genetic mutations including in SCN1A was negative. Pet. Ex. 17. Afterwards, respondent's expert Dr. Wiznitzer then opined that M.S.M. had a "as of yet-unidentified genetic mutation." Resp. Ex. B at 10. He opined that the first round of testing was "not inclusive of all genetic causes of infantile epileptic encephalopathy." *Id.*

Afterwards, in October 2015, M.S.M. underwent a comprehensive epilepsy panel/ sequencing and deletion/ duplication analysis of 70 genes, which only revealed a single variant of unknown significance (in a gene other than SCN1A). Pet. Ex. 64. The record also provides that a second pathogenic variant would typically be expected and the testing was inconclusive.

Dr. Wiznitzer admitted: "we don't know what [the change in the PKNP gene] represents." Tr. 169.

Dr. Wiznitzer maintained that separate and apart from M.S.M.'s two episodes of status epilepticus, she had a "purely genetic" seizure condition. However, he could not identify the "underlying genetic reason." Tr. 224. The Vaccine Act specifically provides that an alternative cause cannot be "idiopathic, unexplained, unknown, hypothetical, or undocumented." § 13(a)(2). Accordingly, respondent has not met his burden of showing a specific alternative cause for M.S.M.'s condition.[50]

IV. Conclusion

For the aforementioned reasons, petitioner has satisfied her burden of proof. M.S.M.'s vaccines caused an acquired epileptic encephalopathy with sequelae including continued seizure activity and developmental delay. She has satisfied her burden of proof. Accordingly, she is entitled to compensation. A separate damages order will issue.

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master

[50] In Dr. Lobo's reports, he suggested that M.S.M. had a preexisting illness which may have caused her fever which incited the status epilepticus. This was based on medical records indicating that she was ill with cough for some days prior to the vaccine visit, as well as a high lymphocyte percentage on bloodwork obtained at the hospital. Resp. Ex. S at 4; Resp. Ex. EE at 3. However, at the hearing, Dr. Lobo agreed that the vaccines caused M.S.M.'s fever. Tr. 253. Additionally, Dr. Wiznitzer testified that there was no evidence that M.S.M. had a viral infection and that the vaccines caused her fever. Tr. 143. I find that to whatever extent respondent posited that an unspecified viral illness was the more likely alternative cause for M.S.M.'s status epilepticus and resulting injury, he conceded that argument at the hearing.